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SYRINGOMA

HISTOCHEMICAL AND ELECTRON MICROSCOPIC STUDIES*

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The histogenesis of syringoma has been a matter of controversy: does it represent an organoid growth of eccrine (1, 2, 3) or apocrine (4, 5, 6) structures and, further, is its differentiation in the direction of ductal or glandular structures. The present investigation was designed to clarify these two problems.

MATERIALS AND METHODS

Specimens were obtained from five individuals with syringoma. In addition, the skin from the sole and axilla of five human embryos ranging from 7 to 15 cm in crown-rump length (13 to 24 weeks old) was used, as was normal axillary skin from seven volunteers and skin from one case of erythema multiforme showing regeneration of the epidermis. Fresh frozen sections were used for histochemical stains which included amylophosphorylase (7), branching enzyme (7), succinic dehydrogenase (8), leucine aminopeptidase (9), PAS (10), indoxyl esterase (11), acid phosphatase (12), alkaline phosphatase (8) and β-glucuronidase (13). Small blocks of tissue were embedded in Araldite and sections were studied with an RCA EMU-3G electron microscope.

RESULTS

1. Histochemical Studies

A histochemical comparison of syringoma with adult eccrine and apocrine structures (Table I) revealed a striking similarity of the enzymatic reactions in syringoma and in adult eccrine structures (Fig. 1 a–d). Amylophosphorylase, branching enzyme (Fig. 1a) and succinic dehydrogenase, which reacted intensely in eccrine structures and weakly to negative in apocrine structures, gave a moderate to intense reaction in syringoma. Leucine aminopeptidase gave the same reaction with the exception that the apocrine secretory segment also stained moderately.

The PAS reaction varied from specimen to specimen depending on the functional status of the individual eccrine and apocrine structures; but on the average it was stronger in eccrine than in apocrine structures. Although some of the granules present within the apocrine secretory segment stained intensely with the PAS reaction, the majority of granules and the rest of the cytoplasm reacted weakly. The lesions of syringoma stained intensely with the PAS stain. Treatment with diastase diminished the intensity of the PAS stain in all tissues except the apocrine duct in which most of the stain was removed, indicating that most of the positive PAS reaction there had been due to the presence of glycogen.

Acid phosphatase reacted intensely in apocrine structures and moderately in eccrine structures. The lesions of syringoma reacted similar to the eccrine structures (Fig. 1b).

Indoxyl esterase reacted moderately within the apocrine secretory segment. In all other structures including the lesions of syringoma the reaction was faint to negative.

Alkaline phosphatase was intensely reactive in the myoepithelial cells of both the eccrine and the apocrine secretory segments. On the other hand, no staining reaction was visible in the lesions of syringoma, indicating that few if any myoepithelial cells were present (Fig. 1c and d).

The reaction for β-glucuronidase was so intense in both eccrine and apocrine secretory segments that the final reaction product diffused into the surrounding stroma. The reaction was of moderate intensity in both eccrine and apocrine ducts. The lesions of syringoma also stained moderately.

In the eccrine and apocrine glands of the human embryo the reactions for the enzymes

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TABLE I

Patterns of enzymatic reactions in syringoma and in adult eccrine and apocrine glands

	Syringoma	Eccrine duct	Eccrine secretory segment	Apocrine duct	Apocrine secretory segment
Amylophosphorylase and branching enzyme	++++	++++	++++	+	−
Succinic dehydrogenase	++	+++	+++	−	+
Leucine aminopeptidase	+++	+++	++++	+	++
PAS	++++	+++	++++	+++	some granules ++++
Diastase-resistant PAS	+++	++	+++	+	+
	lumen ++++	cuticle +++	lumen ++++	cuticle ++	lumen ++
Acid phosphatase	++	++	++	+++	++++
Indoxyl esterase	−	+	+	−	++
Alkaline phosphatase	−	−	−	−	−
			myoepithelial ++++ cells		myoepithelial ++++ cells
β-glucuronidase	+++	+++	++++	++	++++

− structure not observed; + weak reaction; ++ moderate reaction; +++ strong reaction; ++++ very strong reaction.

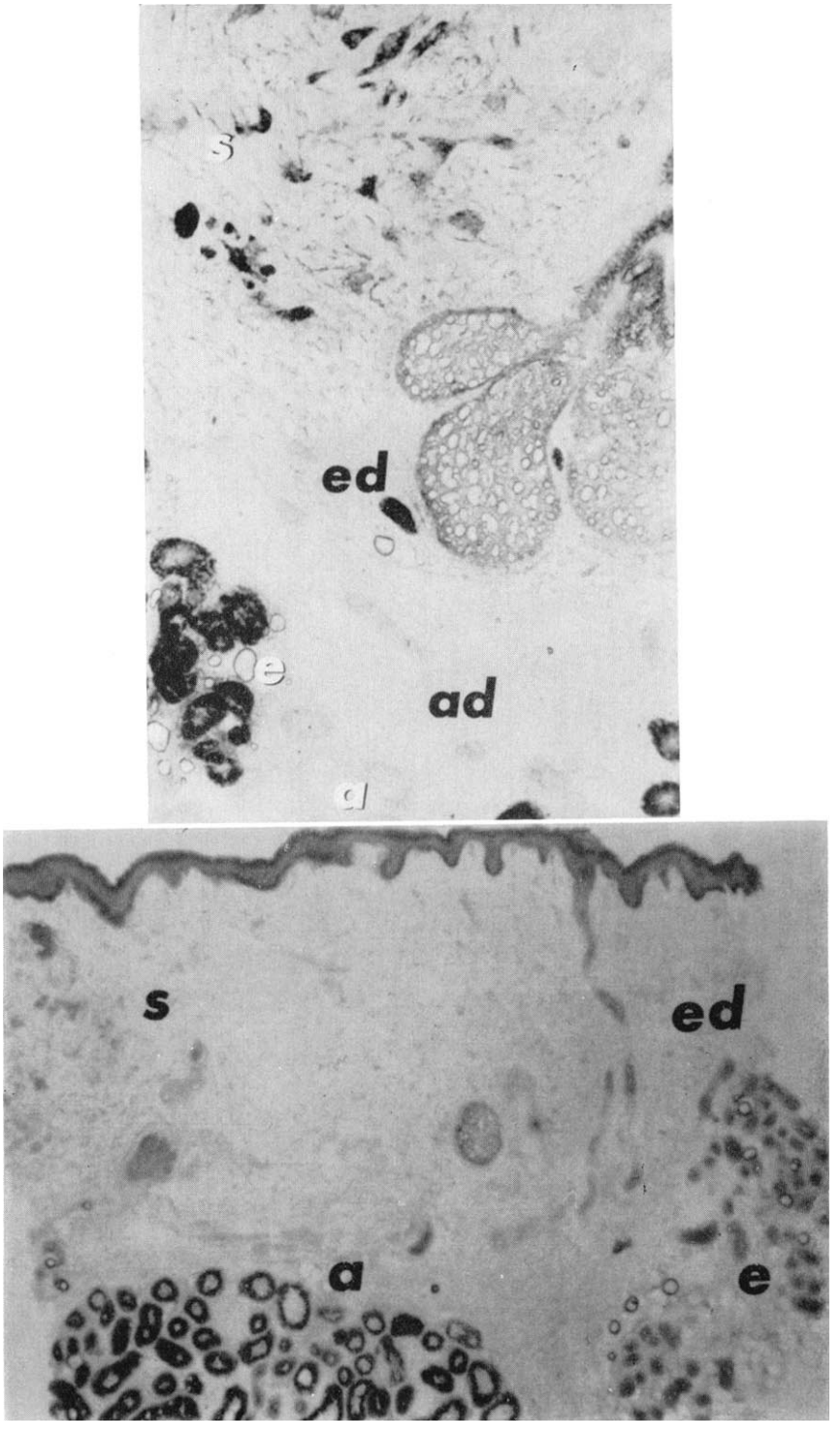

FIG. 1. *Apocrine and eccrine glands and syringoma in the axillary region. a.* Reaction for amylophosphorylase and branching enzyme. *a* (aprocrine secretory segment) −; *ad* (apocrine duct) 1+; *e* (eccrine secretory segment) 4+; *ed* (eccrine duct) 4+; *s* (syringoma) 4+. (× 150.) b. Reaction for acid phosphatase. a (apocrine secretory segment) 4+; *e* (eccrine secretory segment) 2+; *ed* (eccrine duct) +2; *s* (syringoma) 2+. (× 100.) c. Reaction for alkaline phosphatase in eccrine and apocrine secretory segments. c (capillary walls) 4+; *m* (myofibrils of myoepithelial cell) 4+; *a* (apocrine secretory cells) −; *e* (eccrine secretory cells) −. (× 200.) d. Reaction for alkaline phosphatase in syringoma. The lesions of syringoma (*s*) do not contain positively staining myoepithelial cells. All positively staining areas represent capillaries (*c*). (× 200.)

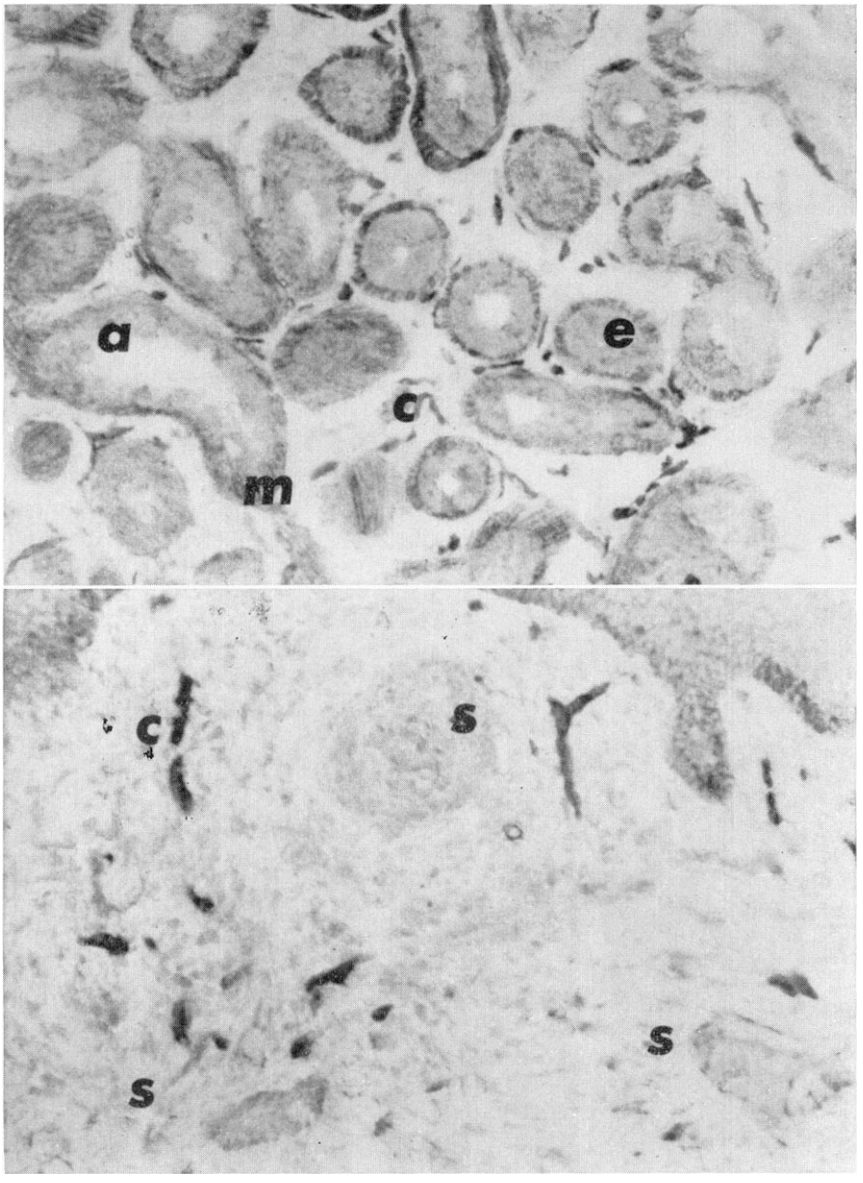

FIG. 1C & D.

were similar to those observed in the adult eccrine and apocrine glands. In particular, the reactions for amylophosphorylase, branching enzyme, succinic dehydrogenase and PAS in the eccrine and apocrine glands of the embryo followed the staining patterns of the adult glands so that eccrine structures could be readily distinguished from apocrine structures in the embryo. Serri, Montagna and Mescon (14), who had studied the reactions for glycogen and amylophosphorylase in the skin of the human embryo, also had been able to differentiate eccrine from apocrine structures by these reactions.

2. Electron Microscopic Studies

a. *Syringoma.* Electron microscopic examination, carried out on several lesions of each of the five cases of syringoma, revealed lumina surrounded by one layer of inner cells and by two or more layers of outer cells. The inner cells, in cross-sections of the duct, appeared elongated, with their long axis parallel to the lumen. The luminal border of the inner cells was lined with numerous short microvilli (Fig. 2). The lateral plasma membranes were markedly convoluted and the convolutions interdigitated with those of neighboring inner and outer cells. Desmosomes were seen between the cells. The outer cells did not differ significantly from the inner cells except for the absence of luminal villi and the presence of more tonofibrils. A continuous basement membrane surrounded each tumor mass (Fig. 2). Occasionally, bundles of collagen fibrils were seen sequestered from the surrounding dermis and trapped between cells of the tumor mass (Fig. 3). Myoepithelial cells, recognizable by their prominent myofibrils, were but rarely found (Fig. 3).

The inner cell nucleus was oblong conforming to the shape of the cell. There was perinuclear clear zone in which many mitochondria and other organelles were embedded. Loosely packed tonofilaments surrounded the nucleus. They extended to the luminal border forming periluminal filamentous zone. The microvilli studding the luminal border also contained tonofilaments. The wide periluminal filamentous zone contained myriads of small clear vesicles. In many areas grouped vesicles surrounded by a membrane developed into multivesicular dense bodies. Some of the multivesicular dense bodies showed one or more cristae (Fig. 4).

The lumina contained a few multivesicular dense bodies and numerous small clear vesicles, especially near and between the microvilli (Fig. 2). Most of the clear vesicles within the lumina appeared identical to those in the periluminal filamentous zone. Some elongated, moderately electron dense vesicles located near the luminal border, however, seemed to represent pinched-off microvilli (Fig. 5).

b. *Comparison of Syringoma with Eccrine and Apocrine Glands.* All features described above for syringoma were found in the embryonic eccrine duct of the lower epidermis* (Fig. 6) (Table II). The adult eccrine duct of the lower epidermis* (Fig. 7) showed the same features as syringoma and the embryonic eccrine duct in the lower epidermis except that fewer multivesicular dense bodies were present in the periluminal filamentous zone.

The embryonic eccrine duct of the dermis had small clear vesicles and pinched-off portions of intraluminal villi were seen but less than in syringoma or in the embryonic eccrine duct of the lower epidermis; and as the most important difference, there were no multivesicular dense bodies.

The embryonic and adult eccrine secretory segments (Fig. 8) did not resemble syringoma at all since the cylindrical luminal cells (secretory cell) of both embryonic and adult eccrine glands showed a light periluminal zone free of tonofilaments, no multivesicular dense bodies and a luminal border with sparse, tall villi.

The embryonic and adult apocrine ducts (Fig. 9) showed less microvilli and less pinching-off than seen in syringoma. There were no multivesicular dense bodies in the periluminal filamentous zone.

The embryonic and adult apocrine secretory segments (Fig. 10) did not show any resemblance to syringoma since there were neither a periluminal filamentous zone, nor multivesicular dense bodies. The luminal border showed sparse, tall villi and a slight degree of pinching-off.

In regenerating epidermis, as it was seen extending along the base of a bulla of erythema multiforme, the eccrine sweat duct was observed to form in a similar manner as the embryonic eccrine duct in the lower epidermis: that is by intracytoplasmic cavity formations. There were numerous small clear vesicles and microvilli at the luminal border, pinched-off portions of microvilli in the lumen and numerous multivesicular dense bodies in the cytoplasm of the inner cells (Fig. 11).

DISCUSSION

Winkelmann and Gottlieb (3), on the basis of their histochemical studies, suggested that syringoma was a tumor with eccrine differentiation. Their findings were confirmed in this

* The lower epidermis includes sweat duct ridge.

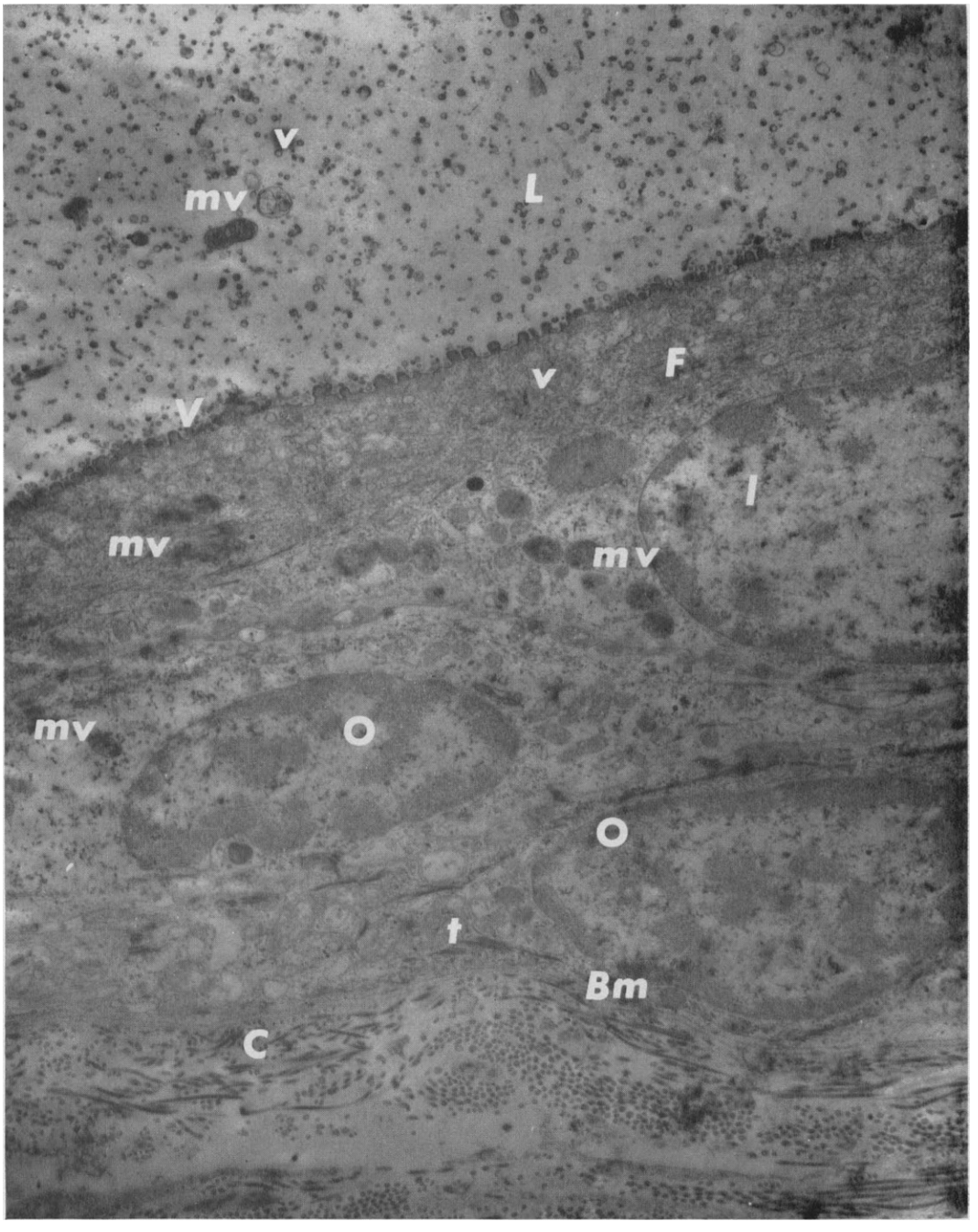

FIG. 2. Syringoma. The lumen (*L*) is surrounded by one layer of inner cells (*I*) with numerous microvilli (*V*) and by two layers of outer cells (*O*). Multivesicular dense bodies (mv) and numerous small clear vesicles (*v*) are present in the lumen. Both are also found in abundance within the inner cells (*I*) and, to a lesser degree, within the outer cells (*O*). *Bm:* basement membrane. *C:* collagen. *F:* periluminal filamentous zone. *t:* bundles of tonofilaments. (× 11,100)

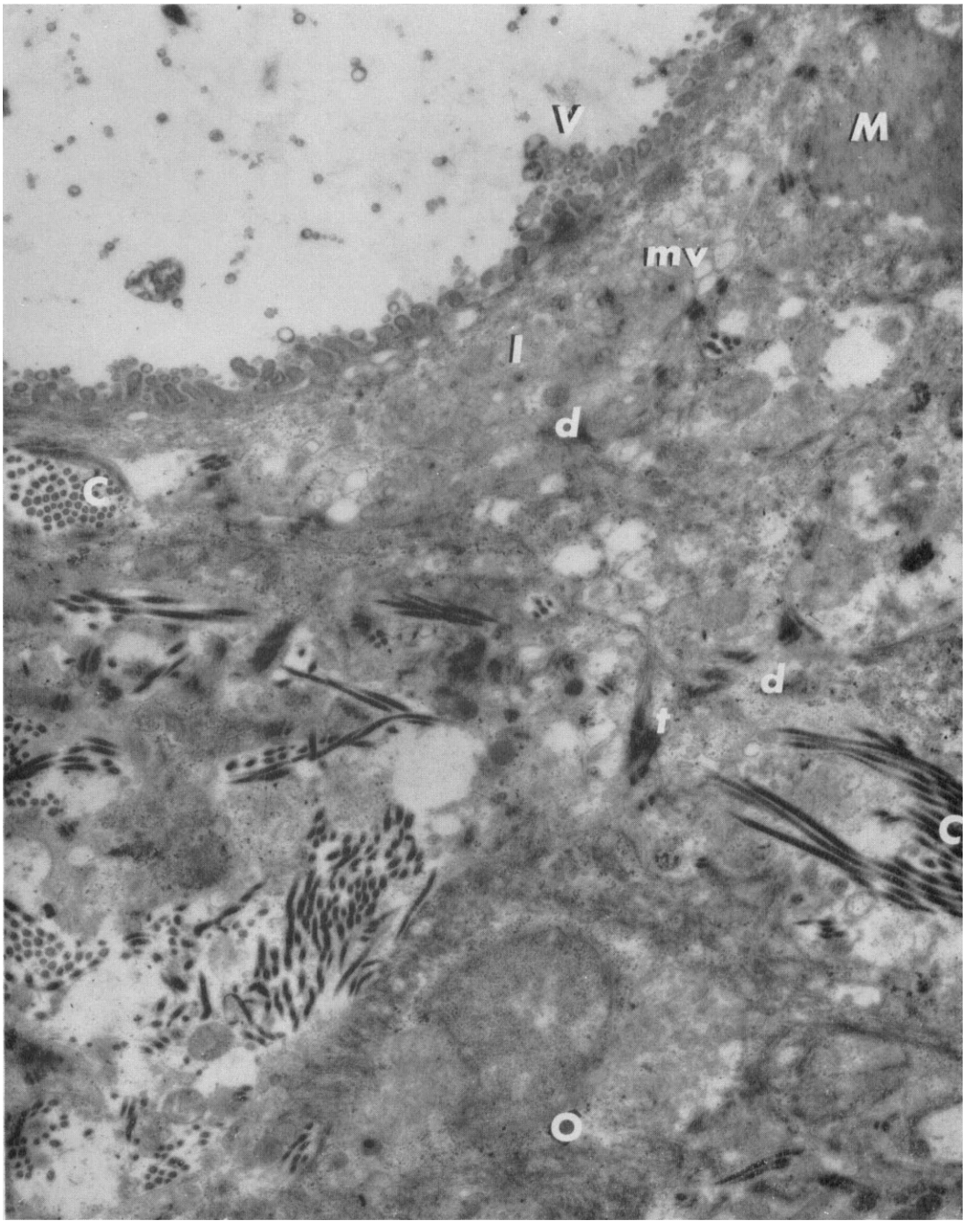

FIG. 3. *Syringoma*. Bundles of collagen fibrils (*C*) lie between the tumor cells. A myoepithelial cell (*M*) is visible in the right upper corner. *d:* desmosomes. *I:* inner cell. *O:* outer cell. *mv:* multivesicular dense bodies. *t:* bundles of tonofilaments. *V:* microvilli. (× 14,800)

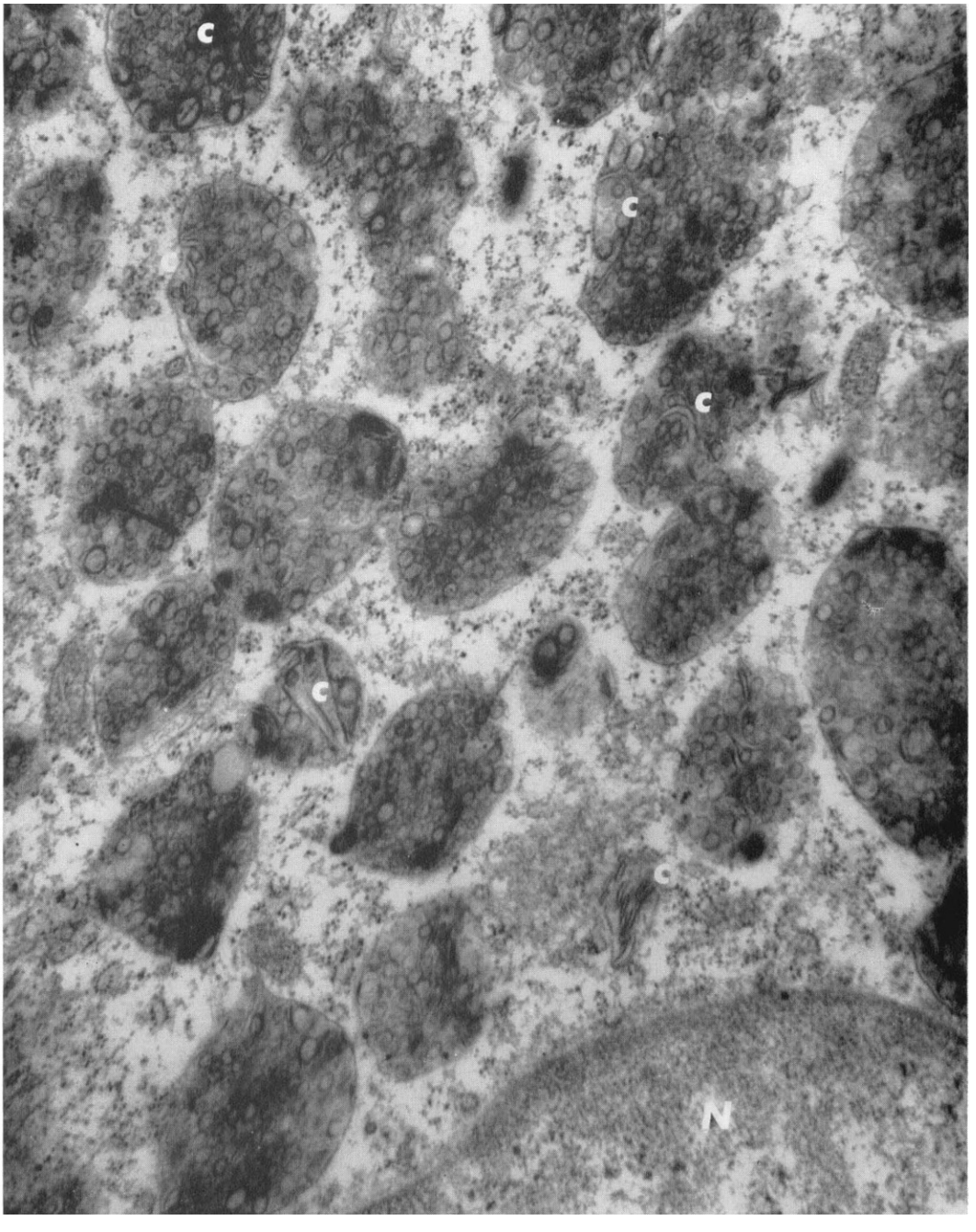

FIG. 4. *Syringoma.* Multivesicular dense bodies are found in abundance in the cytoplasm of an inner cell. They are enveloped by an electron dense membrane. Some of the bodies show thick cristae (*c*). *N:* nucleus. (× 33,580)

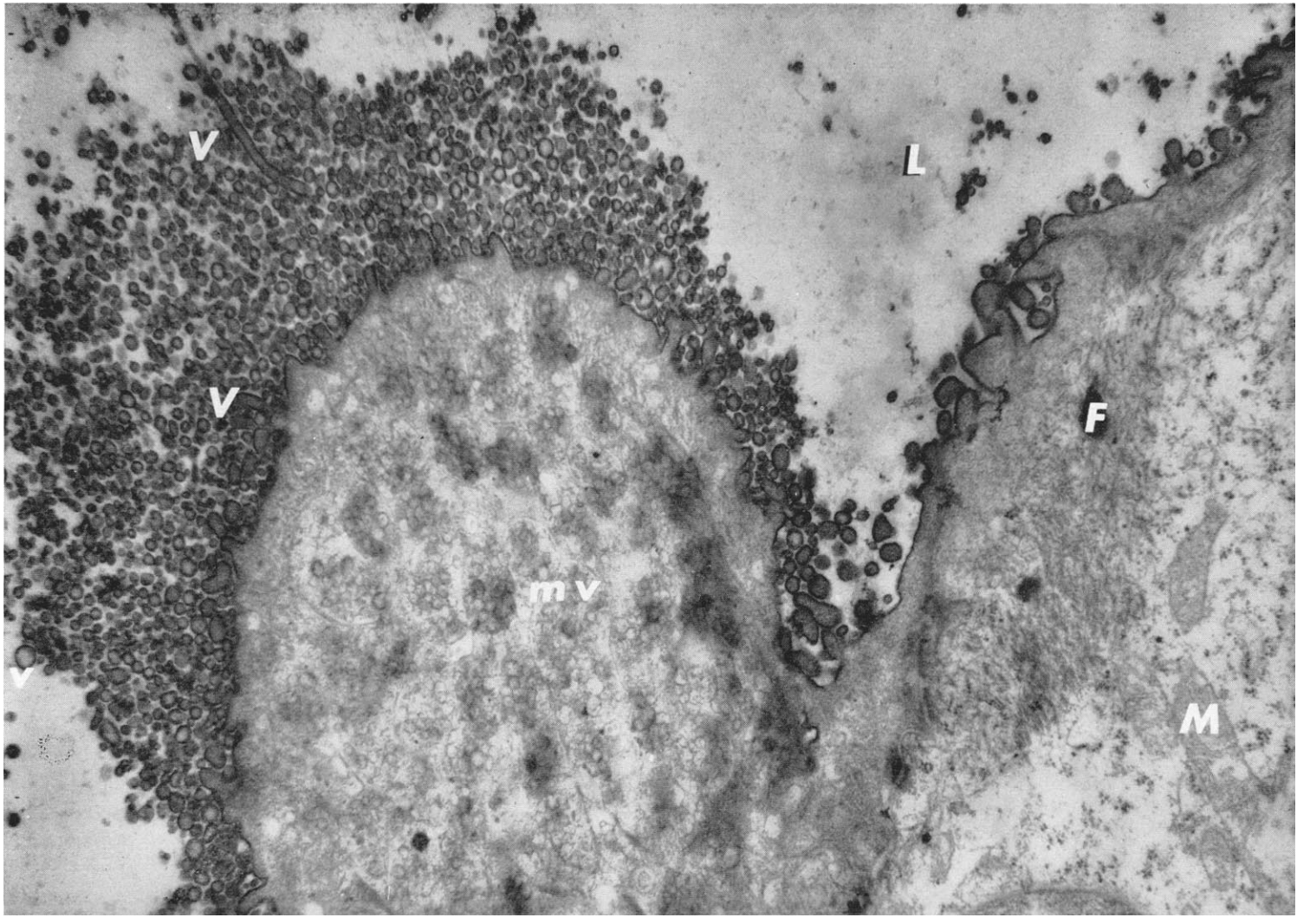

FIG. 5. *Syringoma.* Pinching-off of luminal microvilli is suggested by the presence of numerous microvilli (*V*) within the lumen (*L*). The pinched-off microvilli intermingle with small clear vesicles (*v*). *F:* periluminal filamentous zone. *M:* mitochondria. *mv:* multivesicular dense bodies. (× 26,560)

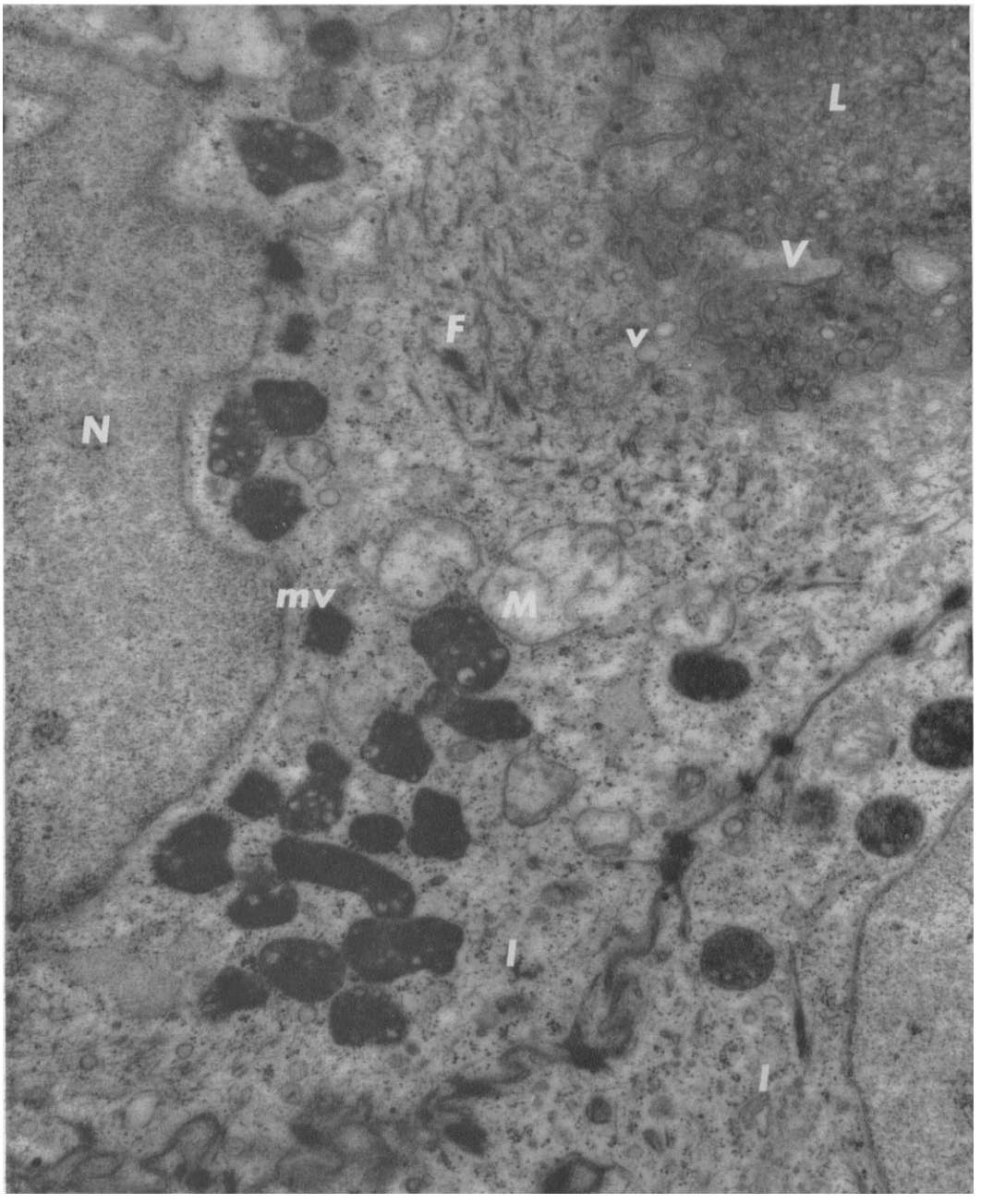

FIG. 6. *Intraepidermal eccrine sweat duct in an embryo (18 cm., 22 weeks).* The duct is cut in the right upper corner revealing lumen (*L*). Inner cells (*I*) contain an abundant amount of multivesicular dense bodies (*mv*). The luminal border shows a filamentous zone (*F*) in which numerous clear vesicles (*v*) are embedded. Similar vesicles are seen near the luminal microvilli (*V*), some of which are pinched-off in the lumen. *M:* mitochondria. *N:* nucleus of inner cell. (× 22,400)

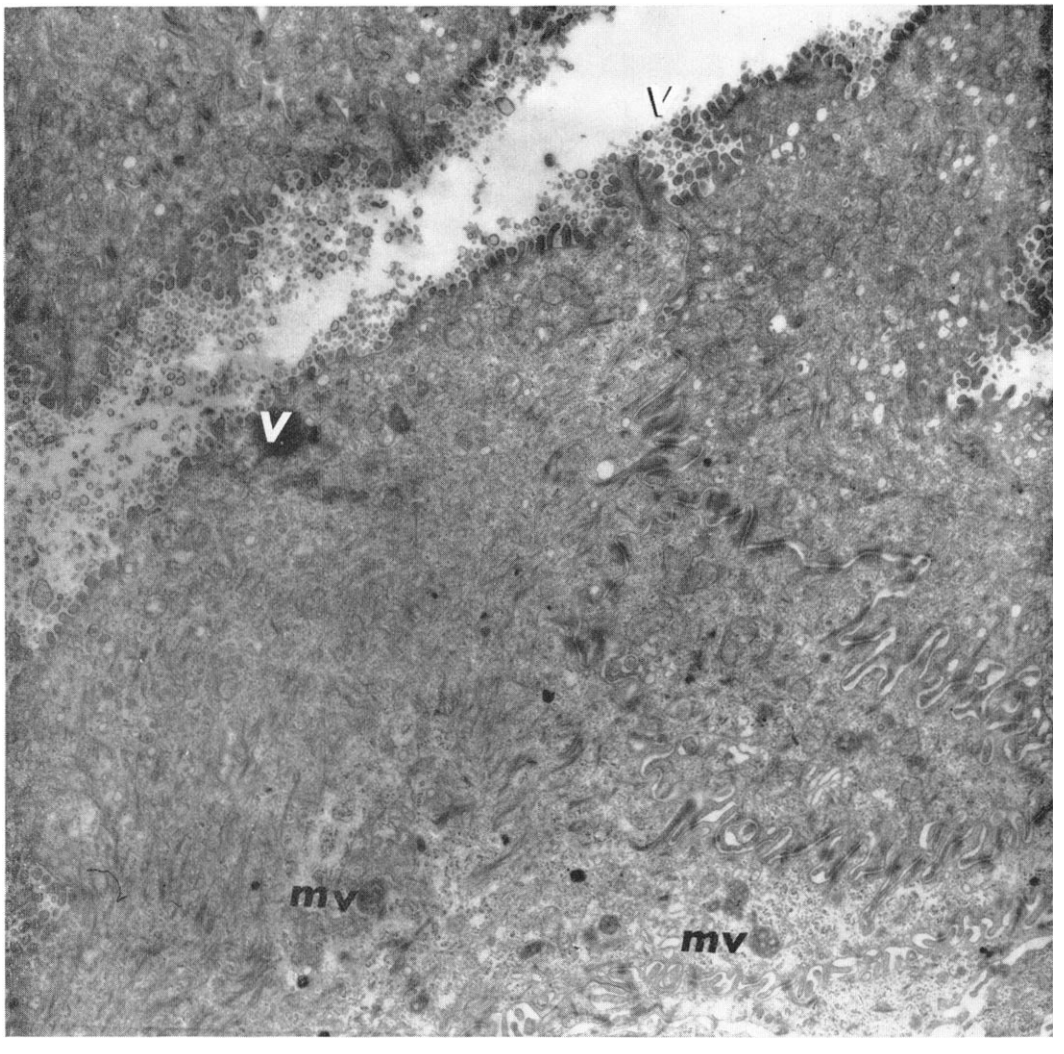

FIG. 7. *Adult eccrine sweat duct in the sweat duct ridge.* The luminal border of the inner cells has numerous microvilli (*V*). The lumen contains pinched-off microvilli. There are several multivesicular dense bodies (*mv*). (× 8,140)

TABLE II

Ultrastructural differentiation of the luminal border of eccrine and apocrine glands

	Villi	Pinching off	Multivesicular dense bodies	Periluminal filamentous zone	Myoepithelial cell
Syringoma	++++	++++	++++	+++	–
Embryo eccrine duct in lower epidermis	++++	++++	++++	+++	–
Adult eccrine duct in lower epidermis	+++	+++	+	++++	–
Regenerating eccrine duct in epidermis	+++	++	++++	+++	–
Embryo eccrine duct in dermis	++	++	–	+	–
Embryo eccrine secretory segment	+	+	–	–	–
Adult eccrine secretory segment	++	+	–	–	++++
Embryo apocrine duct	+	+	–	+	–
Adult apocrine duct	++	+	–	+++	–
Embryo apocrine secretory segment	+	+	–	–	–
Adult apocrine secretory segment	++	+	–	–	++++

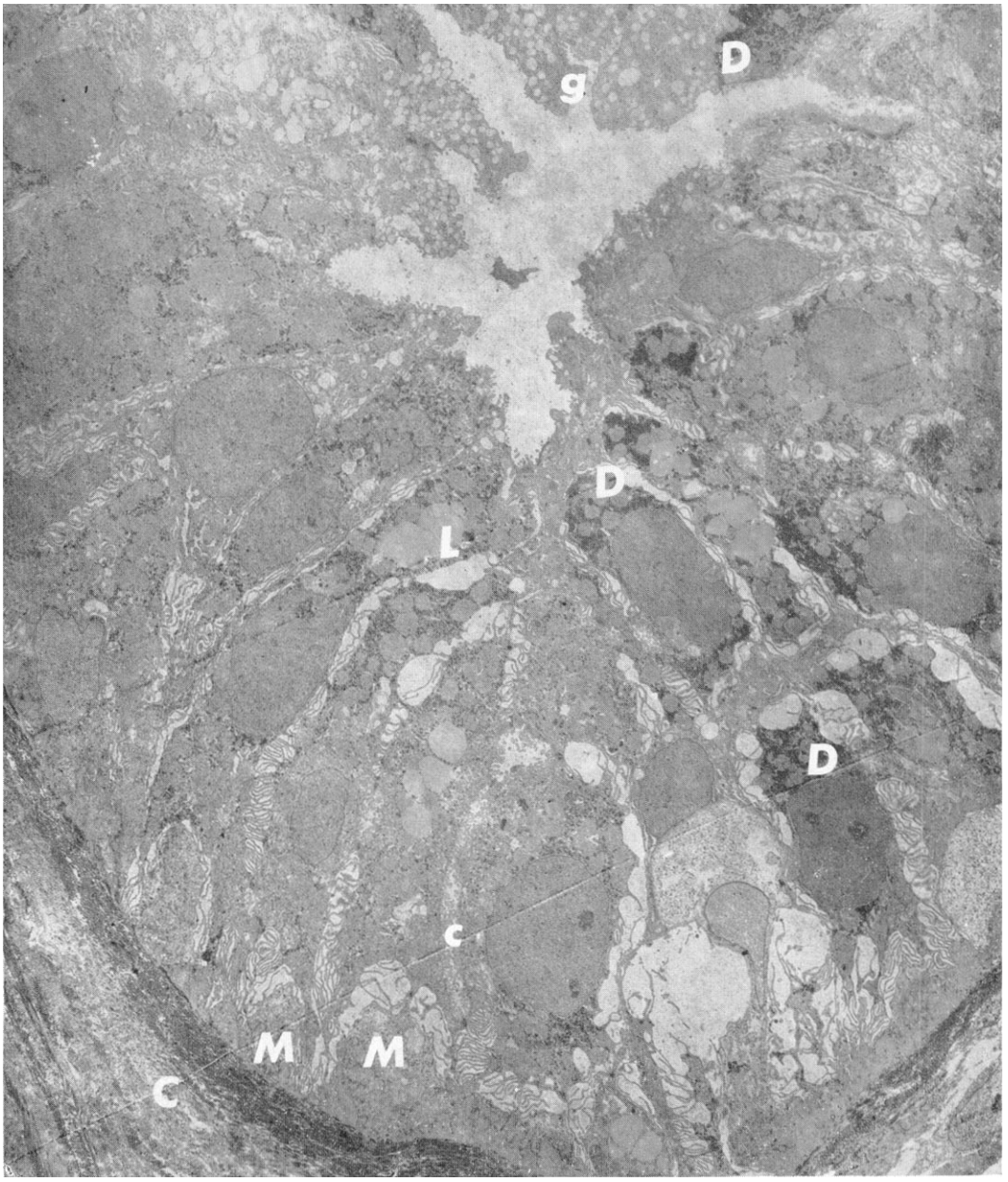

FIG. 8. *Adult eccrine gland.* The adult eccrine gland is composed of myoepithelial cells (*M*), glycogen-laden dark appearing cells (*D*) and less-glycogen containing light appearing cells (*L*). The luminal borders of these cells have scattered villi. *C:* collagen. *c:* intercellular canaliculi. *g:* secretory granules.

study. Staining for additional enzymes, such as branching enzyme, succinic dehydrogenase and β-glucuronidase, as well as our histochemical studies of embryonic eccrine and apocrine structures support the theory of eccrine differentiation in syringoma.

The electron microscopic studies revealed a marked similarity between the luminal border

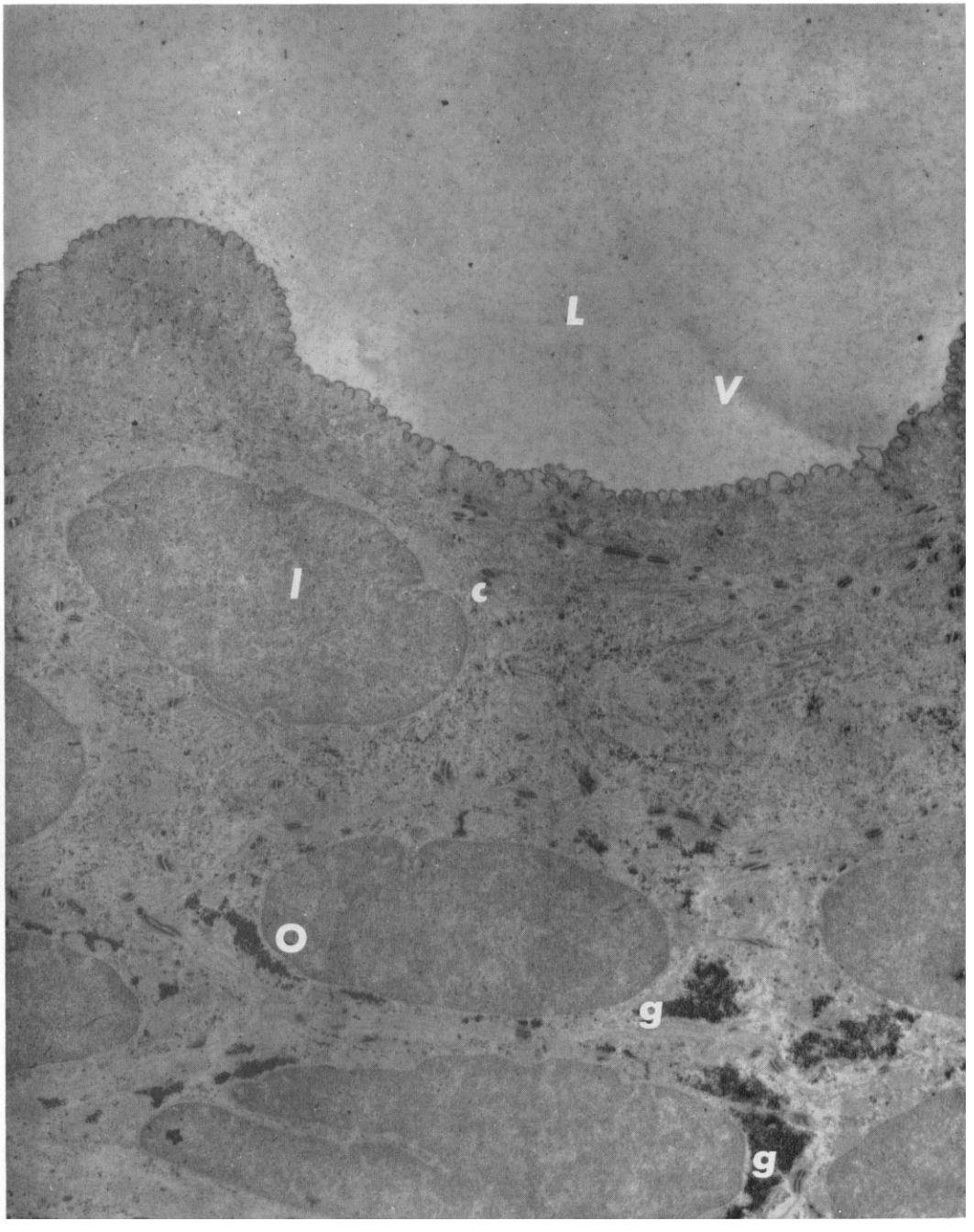

FIG. 9. *Adult apocrine duct.* Luminal microvilli (*V*) are poorly developed and scanty. Outer cells (*O*) contain abundant amounts of glycogen granules (*g*). L: lumen: *I:* inner cell. *c:* perinuclear clear zone. (× 8,140)

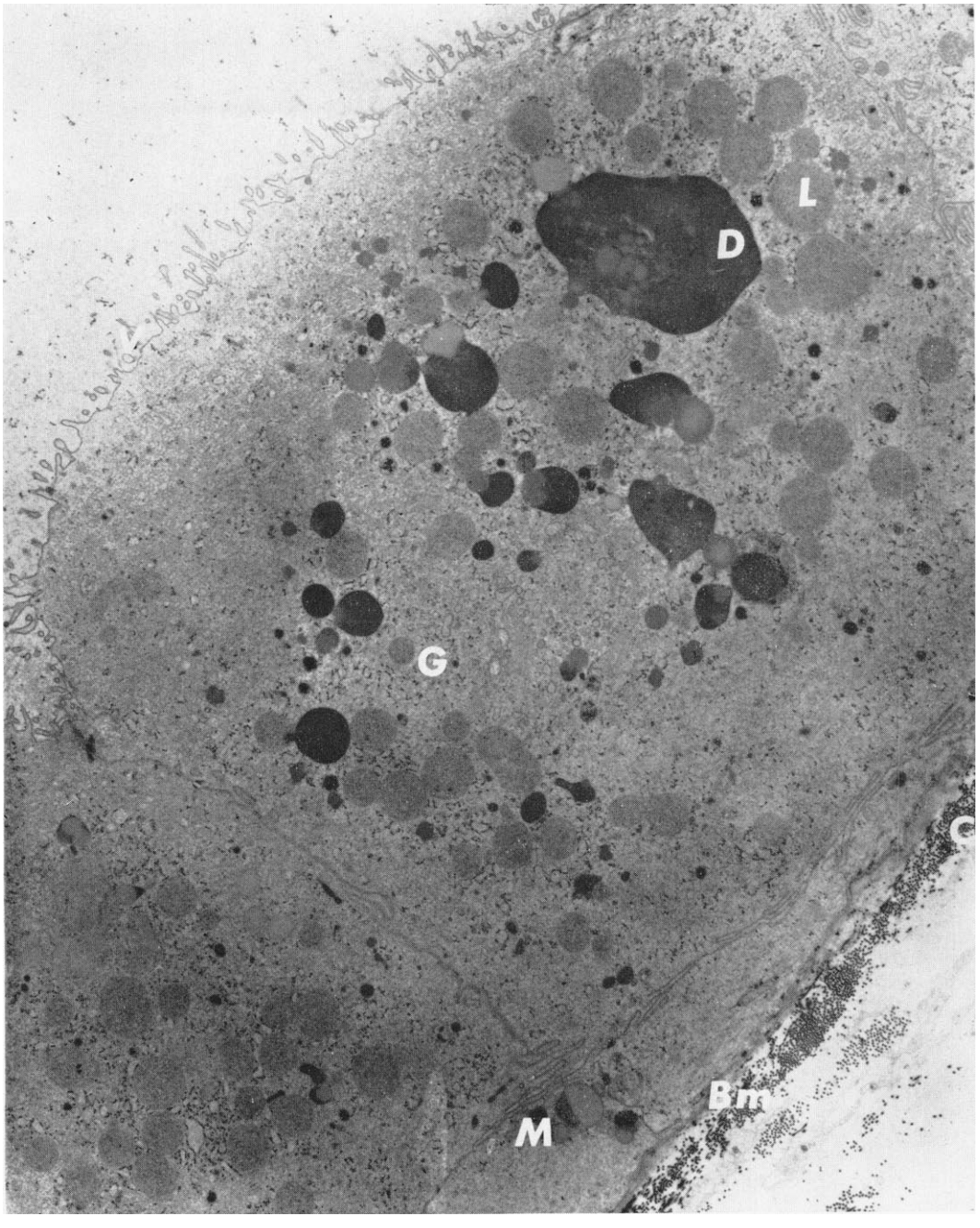

FIG 10. *Adult apocrine secretory segment.* The adult apocrine secretory segment has myoepithelial cells (*M*) and secretory cells with both dark (*D*) and light (*L*) secretory granules. The luminal border of the secretory cells bears slender microvilli (*V*). *G:* Golgi apparatus. *Bm:* basement membrane. *C:* collagen. (× 8,030)

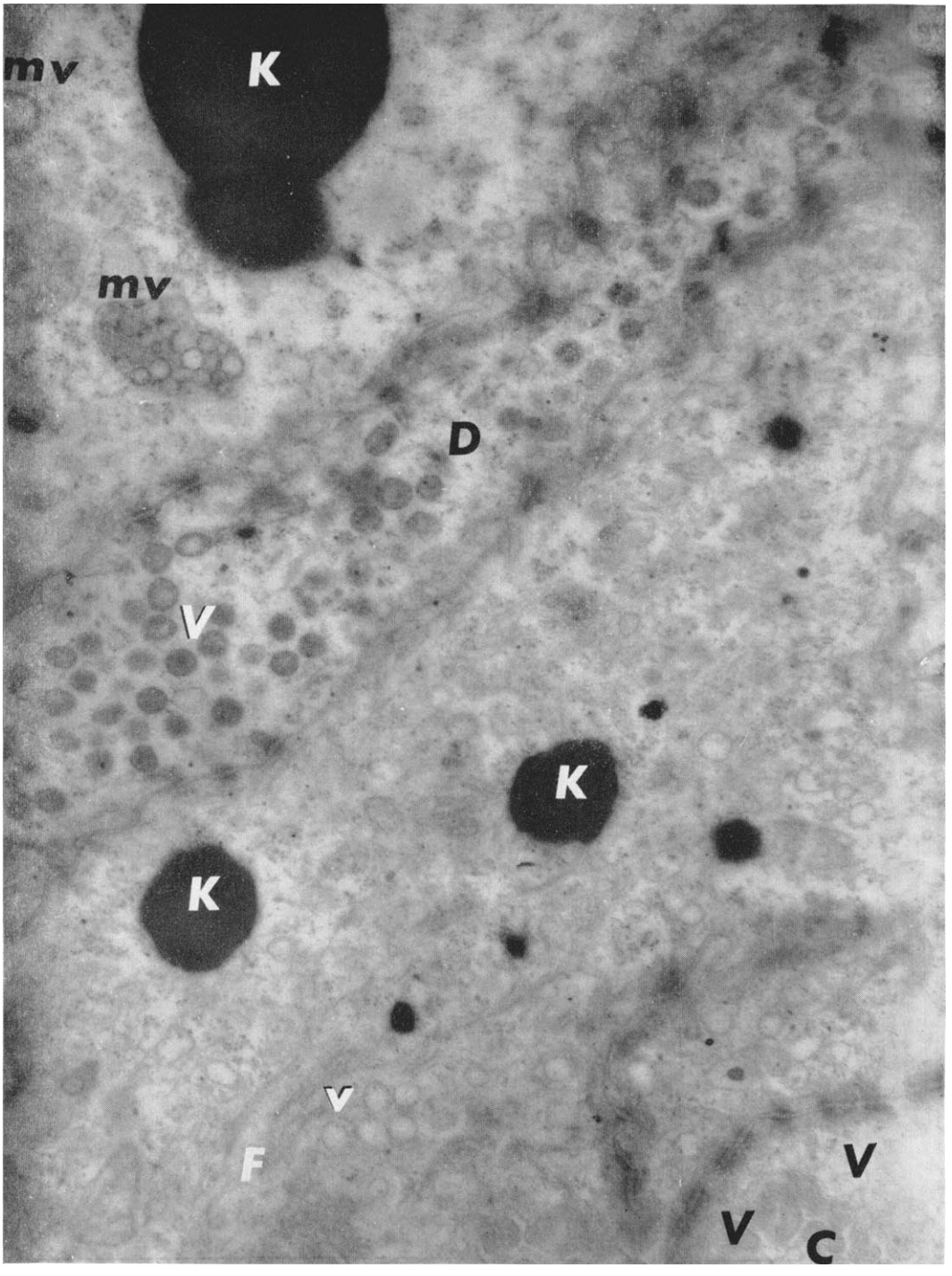

FIG. 11. *Re-formation of an intraepidermal eccrine duct in the regenerating epidermis in erythema multiforme.* There are intracytoplasmic cavities (*C*). Clear vesicles (*v*) are seen in the periluminal fibrous zone (*F*). Borders of the cavities have numerous microvilli (black *V*). Several multivesicular dense bodies (*mv*) are seen in the inner cell. *D:* desmosomes. *K:* keratohyalin granules. White *V:* dense vesicles. (× 28,800)

of the inner cells of syringoma and the luminal border of the embryonic eccrine sweat duct in the process of formation, as seen in the lower epidermis. The pronounced pinching-off of luminal microvilli and the presence of multivesicular dense bodies were common to both syringoma and the embryonic eccrine duct.

The formation of the embryonic eccrine sweat duct in the epidermis is initiated by the appearance of cavities within the cytoplasm of apposing inner cells (15). The intracellular cavities form and subsequently enlarge by means of an autolytic resolution of the cytoplasm. The cavities then break through the plasma membrane of apposing inner cells and coalesce with one another to form the sweat duct (15). The multivesicular dense bodies present in the inner cells probably are lysosomes since they contain acid phosphatase, β-glucuronidase and PAS-positive, diastase-resistant material (16). Inasmuch as lysosomes play an important part in autolysis (16, 17), it is likely that they induce the autolytic formation of the ductal cavities (15). Finding of the same multivesicular dense bodies in the regenerating epidermis of erythema multiforme during the autolytic re-formation of the eccrine sweat duct, corroborates our contention that the multivesicular dense bodies are lysosomes.

The multivesicular dense bodies present in syringoma probably are also lysosomes, since acid phosphatase, β-glucuronidase, PAS-positive, diastase-resistant substance were detected in the syringoma lesions. Their presence in syringoma indicates that in syringoma the ductal structures are formed in the same way as the eccrine sweat ducts are formed in the epidermis, either during the initial formation in the lower epidermis of the embryo or during reformation in the epidermis after injury.

The presence of myoepithelial cells and of bundles of collagen fibers in the wall surrounding the lumina of syringoma may indicate some degree of glandular differentiation; but since myoepithelial cells were extremely rare the evidence still suggests a predominantly ductal differentiation of the tumor.

SUMMARY

Histochemical examination revealed that amylophosphorylase, branching enzyme, succinic dehydrogenase, leucine aminopeptidase and PAS-positive material, all of which are present in higher concentration in eccrine than in apocrine structures, were strongly reactive in syringoma. On the other hand, acid phosphatase and indoxyl esterase, both of which show a stronger reaction in apocrine than in eccrine structures, were negative and moderate in reaction in syringoma. Alkaline phosphatase, present in the myoepithelial cells of both eccrine and apocrine glands, was absent in the lesions of syringoma. On the basis of the histochemical findings it was concluded that syringoma is an organoid tumor differentiating in the direction of eccrine structures.

Electron microscopic examination revealed the lumina of syringoma to be bordered by numerous short microvilli. Innumerable small vesicles and pinched-off portions of microvilli were present in the lumina. A number of multivesicular dense bodies were embedded in the periluminal filamentous zone of the inner cells.

Multivesicular dense bodies and pronounced pinching-off of villi were also found in the embryonic and adult eccrine duct of the lower epidermis. Multivesicular dense bodies were absent in embryonic and adult apocrine structures. Therefore, it was concluded that the differentiation in syringoma is in the direction of eccrine sweat ducts.

It has been postulated that the multivesicular dense bodies found in syringoma represent lysosomes.

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